

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
 United States Patent and Trademark
 Office
 Box PCT
 Washington, D.C.20231
 ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 22 February 2000 (22.02.00)	
International application No. PCT/GB99/02044	Applicant's or agent's file reference IS/CP5787577
International filing date (day/month/year) 29 June 1999 (29.06.99)	Priority date (day/month/year) 29 June 1998 (29.06.98)
Applicant LEADLAY, Peter, Francis et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
 27 January 2000 (27.01.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Juan Cruz Telephone No.: (41-22) 338.83.38
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The first of these is the fact that the
 government has been unable to
 maintain a stable currency. This
 has led to a loss of confidence
 in the government and a
 consequent loss of support
 from the people. The second
 is the fact that the government
 has been unable to maintain
 a stable economy. This has
 led to a loss of confidence
 in the government and a
 consequent loss of support
 from the people. The third
 is the fact that the government
 has been unable to maintain
 a stable society. This has
 led to a loss of confidence
 in the government and a
 consequent loss of support
 from the people.

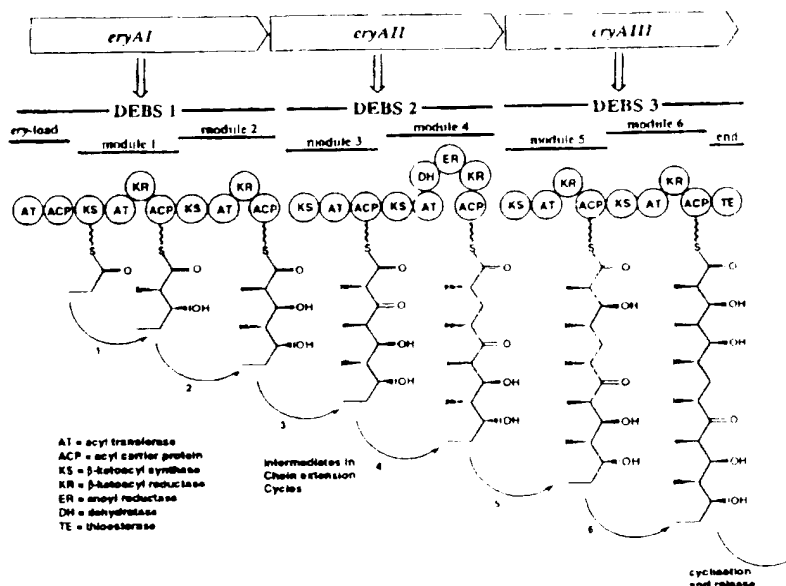
The fourth is the fact that the
 government has been unable to
 maintain a stable foreign
 policy. This has led to a
 loss of confidence in the
 government and a consequent
 loss of support from the
 people.



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C12N 15/52, 15/62, 9/00, 15/81, 1/19, C12P 19/62		A3	(11) International Publication Number: WO 98/01546
			(43) International Publication Date: 15 January 1998 (15.01.98)
(21) International Application Number: PCT/GB97/01819		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 4 July 1997 (04.07.97)		Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	
(30) Priority Data: 9614189.0 5 July 1996 (05.07.96) GB 60/024,188 19 August 1996 (19.08.96) US 9710962.3 28 May 1997 (28.05.97) GB		(88) Date of publication of the international search report: 9 April 1998 (09.04.98)	
(71) Applicant (for all designated States except US): BIOTICA TECHNOLOGY LIMITED [GB/GB]; 112 Hills Road, Cambridge CB2 1PH (GB).			
(72) Inventors; and (75) Inventors/Applicants (for US only): LEADLAY, Peter, Francis [GB/GB]; 17 Clarendon Road, Cambridge CB2 2BH (GB). STAUNTON, James [GB/GB]; 29 Porson Road, Cambridge CB2 2ET (GB). CORTES, Jesus [MX/GB]; 26 Cambanks, Union Lane, Cambridge CB4 1PZ (GB).			
(74) Agents: STUART, Ian et al.; Mewburn Ellis, York House, 23 Kingsway, London WC2B 6HP (GB).			

(54) Title: POLYKETIDES AND THEIR SYNTHESIS



(57) Abstract

A hybrid type I polyketide synthase gene typically containing a starter module and a plurality of heterologous extender modules is used to synthesise novel polyketides. It is preferably under the control of a type II polypolyketide synthase promoter e.g. act 1 of *S. coelicolor*.

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EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 97/01819

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/52 C12N15/62 C12N9/00 C12N15/81 C12N1/19
C12P19/62

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C12P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 95 08548 A (LELAND STANFORD JUNIOR UNIVERSITY) 30 March 1995 see page 5, line 1 - page 7, line 12 see page 15, line 21 - page 16, line 32 see page 23, line 22 - page 26, line 15 see page 27, line 12 - page 28, line 2 see page 29, paragraph 1 see page 30, paragraph 2 - page 31, paragraph 1 see page 43, line 25 - page 45, line 4</p> <p style="text-align: center;">--- -/-</p>	1,3,8, 14-23

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex

* Special categories of cited documents

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

18 February 1998

Date of mailing of the international search report

03.03.98

Name and mailing address of the ISA

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Tel. (+31-70) 340-2040, Tx 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Gurdjian, D

INTERNATIONAL SEARCH REPORT

 Intern. Application No
 PCT/GB 97/01819

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	PARRO, VICTOR ET AL: "Transcription of genes involved in the earliest steps of actinorhodin biosynthesis in Streptomyces coelicolor" NUCLEIC ACIDS RES. (1991), 19(10), 2623-7 CODEN: NARHAD;ISSN: 0305-1048, XP002056140 see abstract see page 2626, right-hand column, paragraph 2 - page 2627, paragraph 3 ---	20-22
A	JESUS CORTES ET AL.: "Repositioning of a domain in a modular polyketide synthase to promote specific chain cleavage" SCIENCE, vol. 268, no. 5216, 9 June 1995, LANCASTER, PA US, pages 1487-1489, XP002045167 cited in the application see abstract see page 1487, right-hand column, paragraph 2 - page 1489, left-hand column, last paragraph ---	1-19
A	STEFANO DONADIO ET AL.: "An erythromycin analog produced by reprogramming of polyketide synthesis" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 90, no. 15, 1 August 1993, WASHINGTON US, pages 7119-7123, XP002045168 cited in the application see abstract see page 7119, right-hand column, paragraph 2 see page 7120, right-hand column, paragraph 2; figure 2 see page 7122, right-hand column, paragraph 2 - page 7123, left-hand column, last paragraph ---	1-19
A	WO 93 13663 A (ABBOTT LABORATORIES) 22 July 1993 cited in the application see page 2, line 17 - page 3, line 2 see page 6, line 1 - page 9, line 25 ---	1-19
A	MCDANIEL R ET AL: "CONSTRUCTION OF HYBRID POLYKETIDE SYNTHASES VIA GENE REPLACEMENTS AND ANALYSIS OF POLYKETIDE PRODUCTS." 205TH ACS (AMERICAN CHEMICAL SOCIETY) NATIONAL MEETING, DENVER, COLORADO, USA, MARCH 28-APRIL 2, 1993. ABSTR PAP AM CHEM SOC 205 (1-2). 1993. BIOT 12. CODEN: ACSRAL ISSN: 0065-7727, XP002045169 --- -/--	1-19

INTERNATIONAL SEARCH REPORT

Intern: al Application No

PCT/GB 97/01819

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	KHOSLA, CHAITAN ET AL: "Genetic construction and functional analysis of hybrid polyketide synthases containing heterologous acyl carrier proteins" J. BACTERIOL. (1993), 175(8), 2197-204 CODEN: JOBAAY;ISSN: 0021-9193, 1993, XP002045170 ---	1-19
A	OLIYNYK, MARKIYAN ET AL: "A hybrid modular polyketide synthase obtained by domain swapping" CHEM. BIOL. (1996), 3(10), 833-839 CODEN: CBOLE2;ISSN: 1074-5521, 1996, XP002045171 see page 833, right-hand column, paragraph 2 - page 837, right-hand column, paragraph 2 ---	1-19
A	FERNANDEZ-MORENO M A ET AL: "NUCLEOTIDE SEQUENCE AND DEDUCED FUNCTIONS OF A SET OF COTRANSCRIBED GENES OF STREPTOMYCES COELICOLOR A3(2) INCLUDING THE POLYKETIDE SYNTHASE FOR THE ANTIBIOTIC ACTINORHODIN" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 267, no. 27, 25 September 1992, pages 19278-19290, XP000652285 see the whole document ---	1-23
P,X	KUHSTOSS S ET AL: "Production of a novel polyketide through the construction of a hybrid polyketide synthase" GENE, vol. 183, no. 1, December 1996, page 231-236 XP004062752 see abstract see page 233, left-hand column, paragraph 1 - page 235, left-hand column, paragraph 2 ---	1-5, 14-19
P,X	WO 96 40968 A (UNIV LELAND STANFORD JUNIOR ;JOHN INNES CENTRE (GB)) 19 December 1996 see page 5, line 5 - page 9, line 3 see page 18, line 16 - page 22, line 6 see page 25, line 24 - page 29, line 8 see page 37, line 3 - line 35 see page 38, line 10 - page 39, line 24 see page 51, line 9 - page 52, line 4; examples -----	1-19

INTERNATIONAL SEARCH REPORT

Int. Patent application No.
PCT/GB 97/01819

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons

- 1 ☐ Claims Nos
because they relate to subject matter not required to be searched by this Authority, namely
- 2 ☐ Claims Nos
because they relate to parts of the international Application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically
- 3 ☐ Claims Nos
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6 4(a)

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This international Searching Authority found multiple inventions in this international application, as follows

see additional sheet

- 1 ☒ As all required additional search fees were timely paid by the applicant, this international Search Report covers all searchable claims
- 2 ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee
- 3 ☐ As only some of the required additional search fees were timely paid by the applicant, this international Search Report covers only those claims for which fees were paid, specifically claims Nos
- 4 ☐ No required additional search fees were timely paid by the applicant. Consequently, this international Search Report is restricted to the invention first mentioned in the claims, it is covered by claims Nos

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest
- ☒ No protest accompanied the payment of additional search fees

1. Claims: 1-19

Hybrid polyketide synthase gene, hybrid polyketide synthase thereby encoded, vector and transformed organism containing said gene, method of producing such a transformed organism, use thereof for making a polyketide and polyketide so obtained.

2. Claims: 20-23

Use of a type II PKS promoter to control a heterologous gene and nucleic acid comprising a type II PKS promoter operably linked to a heterologous gene

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No.

PCT/GB 97/01819

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9508548 A	30-03-95	US 5672491 A	30-09-97
		AU 678058 B	15-05-97
		AU 7731794 A	10-04-95
		CA 2171629 A	30-03-95
		EP 0725778 A	14-08-96
		JP 9505983 T	17-06-97
		US 5712146 A	27-01-98
WO 9313663 A	22-07-93	CA 2100791 A	18-07-93
		AU 665526 B	11-01-96
		AU 1245092 A	03-08-93
		EP 0626806 A	07-12-94
WO 9640968 A	19-12-96	US 5712146 A	27-01-98
		AU 6157596 A	30-12-96

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference IS/CP5787577	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/GB 99/ 02044	International filing date (day/month/year) 29/06/1999	(Earliest) Priority Date (day/month/year) 29/06/1998
Applicant BIOTICA TECHNOLOGY LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the International search was carried out on the basis of the International application in the language in which it was filed, unless otherwise indicated under this item.



the International search was carried out on the basis of a translation of the International application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the International application, the International search was carried out on the basis of the sequence listing:



contained in the International application in written form.



filed together with the International application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the International application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.

1



None of the figures.



INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 99/ 02044

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
See FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claim 14 relates to a compound defined by reference to a desirable characteristic, namely a difference related to the side chain provided by the starter unit. The claim covers all compounds having this characteristic, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. Moreover, the initial phase of the search revealed a large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim is impossible. In the present case, the claim so lacks support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for the part of claim 14 which appears to be supported and disclosed, namely the part relating to triketide lactones and 13-methyl-erythromycin as disclosed in examples 3, 5, and 8.



INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/02044

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/52 C12N15/62 C12N9/10 C12P17/06 C12P17/08
C12P19/62 C07K19/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12P C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HITCHMAN T S ET AL.: "Catalytic self-acylation of type II polyketide synthase acyl carrier proteins" CHEMISTRY AND BIOLOGY, vol. 5, no. 1, 15 January 1998 (1998-01-15), pages 35-47, XP000879250 page 45, left-hand column, line 27-39; figure 12B --- -/--	1,2,6, 8-13



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

24 February 2000

Date of mailing of the international search report

13/03/2000

Name and mailing address of the ISA

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Fax: (+31-70) 340-3016

Authorized officer

van de Kamp, M



INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/02044

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JACOBSEN J R ET AL: "Spontaneous priming of a downstream module in 6-deoxyerythronolide B synthase leads to polyketide biosynthesis." BIOCHEMISTRY, vol. 37, no. 14, April 1998 (1998-04), pages 4928-4934, XP002130643 abstract page 4932, right-hand column, line 15 -page 4933, left-hand column, line 17 page 4933, right-hand column, line 41 -page 4934, left-hand column, line 6 ---	1,2,6, 8-13
X	WO 97 02358 A (UNIV LELAND STANFORD JUNIOR ;UNIV BROWN RES FOUND (US)) 23 January 1997 (1997-01-23) example 10 ---	1,2,6, 8-13
X	MARSDEN A F A ET AL.: "Engineering broader specificity into an antibiotic-producing polyketide synthase" SCIENCE, vol. 279, 9 January 1998 (1998-01-09), pages 199-202, XP002131320 figure 1 ---	14
A	WO 98 01546 A (CORTES JESUS ;LEADLAY PETER F (GB); STAUNTON JAMES (GB); BIOTICA T) 15 January 1998 (1998-01-15) cited in the application page 6, line 15 -page 10, line 11 claims 1-6 ---	1-13,15
A	BAO W ET AL.: "Reconstitution of the iterative type II polyketide synthase for tetracenomycin F2 biosynthesis" BIOCHEMISTRY, vol. 37, no. 22, June 1998 (1998-06), pages 8132-8138, XP002130659 page 8137, left-hand column, line 17 -right-hand column, line 20 ---	1-4,6
A	KAKAVAS S J ET AL.: "Identification and characterization of the niddamycin polyketide synthase genes from Streptomyces caelestis" JOURNAL OF BACTERIOLOGY, vol. 179, no. 23, December 1997 (1997-12), pages 7515-7522, XP002130645 page 7518, right-hand column, line 33-49 page 7518, right-hand column, line 55 -page 7520, left-hand column, line 7 figures 4,6 page 7521, right-hand column, line 50 -page 7522, left-hand column, line 25 ---	1-3,5-7
	--- -/--	



C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>LEONARD KATZ: "Manipulation of modular polyketide synthases" CHEMICAL REVIEWS, vol. 97, no. 7, November 1997 (1997-11), pages 2557-2575, XP002103748 ISSN: 0009-2665 page 2565, right-hand column, paragraph C page 2571, right-hand column, paragraph C -page 2573; figure 10</p> <p>----</p>	1-15
A	<p>HOPWOOD D A: "Genetic contributions to understanding polyketid synthases" CHEMICAL REVIEWS, vol. 97, no. 7, November 1997 (1997-11), pages 2465-2497, XP002130647 page 2475, paragraph F1 -page 2477 page 2480, paragraph F5 table 2</p> <p>----</p>	1-15
T	<p>BISANG C ET AL.: "A chain initiation factor common to both modular and aromatic polyketide synthases" NATURE, vol. 401, 30 September 1999 (1999-09-30), pages 502-505, XP002130648 the whole document</p> <p>----</p>	1-15
T	<p>WEISSMAN K J ET AL.: "Origin of starter units for erythromycin biosynthesis" BIOCHEMISTRY, vol. 37, no. 31, August 1998 (1998-08), pages 11012-11017, XP002130649 abstract page 11012 -page 11014, line 6 page 11016, right-hand column, line 3-29</p> <p>-----</p>	1,2,6, 8-13



INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/02044

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9702358	A	23-01-1997	AU 706445 B	17-06-1999
			AU 6542696 A	05-02-1997
			CA 2226221 A	23-01-1997
			EP 0836649 A	22-04-1998
			JP 10510167 T	06-10-1998
			NZ 313383 A	30-08-1999
<hr/>				
WO 9801546	A	15-01-1998	AU 3450997 A	02-02-1998
			AU 3451497 A	02-02-1998
			CA 2259420 A	15-01-1998
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



Applicant's or agent's file reference IS/CP5787577		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
FOR FURTHER ACTION		
International application No. PCT/GB99/02044	International filing date (day/month/year) 29/06/1999	Priority date (day/month/year) 29/06/1998
International Patent Classification (IPC) or national classification and IPC C12N15/52		
Applicant BIOTICA TECHNOLOGY LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 7 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 27/01/2000	Date of completion of this report 26.10.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer van Heusden, M Telephone No. +49 89 2399 8145





**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB99/02044

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-78 as originally filed

Claims, No.:

1-15 as originally filed

Drawings, sheets:

1/13-13/13 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB99/02044

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-13, 15
	No:	Claims	14
Inventive step (IS)	Yes:	Claims	15
	No:	Claims	1-14
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet



Additional remarks to section V:

1. Citations

The documents mentioned in this IPER are numbered as in the International Search Report (ISR), i.e. D1 corresponds to the first document of the ISR etc.

2. Novelty and Inventive step (Article 33(2) and (3) PCT)

- 2.1 The present application discloses the use of KSq (or the related CLF domain from type II PKSs) and ATq in the provision of recombinant PKSs which produce polyketides having a desired starting unit. This is achieved due to the surprising finding that ATq is highly specific for malonyl-CoA and KSq decarboxylates specifically said malonyl to acetyl. It further relates to a process of preparing a type II polyketide using a type II PKS in which the CLF domain is genetically engineered to suppress carboxylating activity.
- 2.2 The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject matter of claim 14 is not novel in respect of e.g. document D4. Figure 1 in D4 discloses a group of polyketides which differ in the side chain of the starter unit, which anticipates the subject matter of claim 14.
- 2.3 The present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject matter of claims 1-13 does not solve the problem posed by the present invention. The posed problem appears to be the provision of a method to avoid the formation of mixtures of polyketides with mixed starter units (both acetate and propionate) and to achieve the specific incorporation of unusual starter units. Due to the vagueness of the word '**substantially**' in claim 1 (see also below under VIII.3), the subject matter of claim 1 covers polyketides having **substantially** a desired starter unit, meaning in fact a mixture of polyketides having mainly one starter unit and minor (not specified) amounts of one or more other starter units. Thus the subject matter of claim 1-13 does not solve the posed problem and therefore cannot be considered inventive.
- 2.4 Moreover, the present application does not satisfy the criterion set forth in Article



33(3) PCT because the subject matter of claims 1, 2, 6 and 8-13 does not involve an inventive step in view of documents D1-D3.

Documents D1-D3 all disclose the loading of malonyl, followed by decarboxylation, by ACP in extension modules (in D2 and D3) or by ACP in the single module of the type II PKS in D1. In the absence of a specification of how loading and decarboxylation of malonyl is achieved (i.e. the technical features of the so-called 'adaptation' of the loading module), the ACP-mediated loading and decarboxylation of malonyl disclosed in D1-D3 falls within the scope of claim 1. The subject matter of claim 1 only differs from the disclosures in D1 in that extension modules are present and from the disclosures in D2-D3 in that at least one extension module is not naturally associated with the loading module effecting decarboxylation. However, these issues do not involve an inventive step with regard to the general knowledge in the prior art on exchanging modules between PKSs complexes (e.g. D5).

Claims 2, 6 and 8-13 do not include any additional matter that could render them inventive as such. Thus they would be allowable only in combination with a novel and inventive main claim.

- 2.5 The subject matter of claim 15, the process of preparing a type II polyketide, is based on the surprising finding that the CLF domain of type II PKS has decarboxylating activity and that this activity can be suppressed by engineering the domain, more specifically by substituting Ala for the active site Gln residue. The cited prior art discloses the CLF domain as having a role in regulating chain length and does not disclose any decarboxylase function of CLF. Therefore an inventive step can be recognized for a process of preparing a type II polyketide that makes use of the suppression of decarboxylase activity of the CLF domain.

3. Industrial applicability (Article 33(4) PCT)

The subject matter of claims 1-15 is industrially applicable.

Additional remarks to section VIII:

The following objections are raised under **Article 6 PCT** concerning the clarity of the



claims:

1. Claims 1-7 and 13 lack clarity in that the term '**system**' is vague in that it is not clear whether these claims refer to a method or a product (a PKS). As a result the category of claims 1 and 13 is ambiguous.
2. Moreover, the subject matter of claim 1 is defined as a result to be achieved: the provided PKS multienzyme is defined by a loading module which is 'adapted' to load malonyl and effect decarboxylation. However, the technical features of this so-called 'adaptation' (in fact the essence of the invention!) are lacking in claim 1. The area defined by the claims should be as precise as the invention allows and the independent claim should specify clearly all of the essential features needed to define the invention. Whether claim 1 refers to a method or a product, it should include the essential technical features which are the inclusion of a KSq domain (or a CLF domain) together with a ATq domain (claims 3-5). Claim 7 refers to the KSq domain in claims 1-3, 5 or 6 and thus further underscores the fact that the PKS of claims 1-3, 5 or 6 must contain a KSq. According to the description (p. 16, l. 4-21) KSq and ATq are together responsible for the highly specific production of propionate starter units (p. 16, l. 6). These essential technical features are lacking in the independent claims.
3. Furthermore, the wording '**substantially exclusively**' in claim 1 is rather contradictory. If a polyketide has **exclusively** a desired starter unit, then it cannot have **substantially** said desired starter unit. Thus said wording renders the claim unclear. Moreover, a polyketide having substantially a desired (unspecified) starter unit can have a certain (unspecified) amount of a different starter unit. Such polyketide would be anticipated by many polyketides in the prior art and it appears that it is in fact this problem of mixed starter units that the invention aims at solving. Thus due to the wording 'substantially' claim 1 does not solve the technical problem posed for the present alleged invention (see above under V.2.3).
4. It is noted that the wording '(unsubstituted)' in claim 1 is entirely optional due to the placement between parenthesis.



**INTERNATIONAL PRELIMINARY
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International application No. PCT/GB99/02044

5. The subject matter of claim 3 lacks clarity in that it isn't supported over the entire breadth of the claim. Whereas the applicants have shown that the presence of a glutamine residue in the active site of the KS domain results in the decarboxylating function, they do not show any evidence that **any other** amino acid residue (other than cysteine) at said active site position would also result in decarboxylating activity. Document D3 provides evidence against the fact that any residue other than cysteine at the active site of KS results in decarboxylating activity: a KS domain in which the active site cysteine was replaced by alanine resulted in the loss of decarboxylating activity (example 10).
6. Claim 8 lacks clarity in that it refers to the DNA of the system of any of claims 1-7, whereas said claims neither define nor even relate to any DNA. Furthermore, the variant is again defined by a result to be achieved and thus lacks a clear definition. Moreover, in the absence of a reference to claim 1 it is not clear to what the wording 'said polyketide' refers. Thus also the PKS multienzyme of claim 8 is undefined. The same objection applies to the nucleic acid and the vector of claims 9 and 10, respectively.
7. Claim 13 comprises multiple categories. Claims should relate to a single category. Furthermore, the polyketide according to claim 13(d) is defined by a result to be achieved, which is considered to lack clarity.
8. The subject matter of claim 14 is absolutely undefined and open-ended: it covers any polyketide.
9. The objection raised above (under item 2) also applies to claim 15: the type II PKS in the cultured organism is defined by a result to be achieved (to suppress the decarboxylating activity of said CLF domain) and lacks the essential features of the invention. Moreover claim 15 lacks clarity in that it is not clear whether the CLF domain of the wildtype PKS of the organism has been genetically engineered or whether an additional PKS containing an engineered CLF domain is introduced into the organism.
10. Page 78 of the description is identical to p. 77.





INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

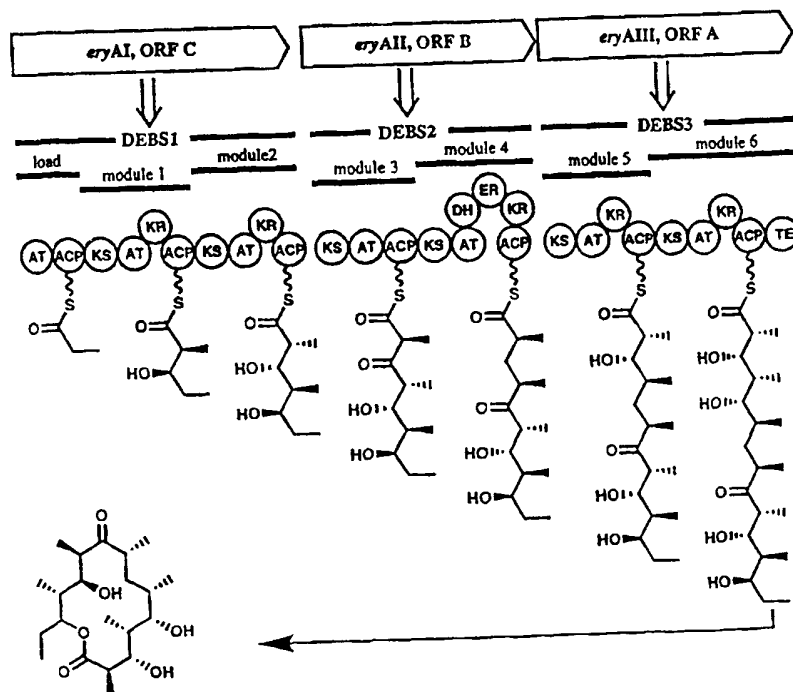
(51) International Patent Classification ⁷ : C12N 15/52, 15/62, 9/10, C12P 17/06, 17/08, 19/62, C07K 19/00		A3	(11) International Publication Number: WO 00/00618
(21) International Application Number: PCT/GB99/02044		(43) International Publication Date: 6 January 2000 (06.01.00)	
(22) International Filing Date: 29 June 1999 (29.06.99)		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(30) Priority Data: 9814006.4 29 June 1998 (29.06.98) GB			
(71) Applicant (for all designated States except US): BIOTICA TECHNOLOGY LIMITED [GB/GB]; 112 Hills Road, Cambridge CB2 1PH (GB).			
(72) Inventors; and (75) Inventors/Applicants (for US only): LEADLAY, Peter, Francis [GB/GB]; 17 Clarendon Road, Cambridge CB2 2BH (GB). STAUNTON, James [ES/GB]; 29 Porson Road, Cambridge CB2 2ET (GB). CORTES, Jesus [GB/GB]; 26 Cambanks, Union Lane, Cambridge CB4 1PZ (GB). McARTHUR, Hamish, Alastair, Irvine [GB/US]; 19 Pheasant Run Drive, Gales Ferry, CT 06335 (US).			
(74) Agents: STUART, Ian et al.; Mewburn Ellis, York House, 23 Kingsway, London WC2B 6HP (GB).			
Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.			
(88) Date of publication of the international search report: 27 April 2000 (27.04.00)			

(54) Title: POLYKETIDES AND THEIR SYNTHESIS

(57) Abstract

A polyketide synthase ("PKS") of Type I is a complex multienzyme including a loading domain linked to a multiplicity of extension domains. The first extension module receives an acyl starter unit from the loading domain and each extension module adds a further ketide unit which may undergo processing (e.g. reduction). We have found that the Ksq domain possessed by some PKS's has decarboxylating activity, e.g. generating (substituted) acyl from (substituted) malonyl. The CLF domain of type II PKS's has similar activity. By inserting loading modules including such domains into PKS's not normally possessing them it is possible to control the starter units used.

The erythromycin PKS





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Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
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INTERNATIONAL SEARCH REPORT

Intern. Appl. No.

PCT/GB 99/02044

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/52 C12N15/62 C12N9/10 C12P17/06 C12P17/08
C12P19/62 C07K19/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12P C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HITCHMAN T S ET AL.: "Catalytic self-acylation of type II polyketide synthase acyl carrier proteins" CHEMISTRY AND BIOLOGY, vol. 5, no. 1, 15 January 1998 (1998-01-15), pages 35-47, XP000879250 page 45, left-hand column, line 27-39; figure 12B --- -/--	1,2,6, 8-13

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "B" document member of the same patent family

Date of the actual completion of the international search

24 February 2000

Date of mailing of the international search report

13/03/2000

Name and mailing address of the ISA

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van de Kamp, M



INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/02044

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JACOBSEN J R ET AL: "Spontaneous priming of a downstream module in 6-deoxyerythronolide B synthase leads to polyketide biosynthesis." BIOCHEMISTRY, vol. 37, no. 14, April 1998 (1998-04), pages 4928-4934, XP002130643 abstract page 4932, right-hand column, line 15 -page 4933, left-hand column, line 17 page 4933, right-hand column, line 41 -page 4934, left-hand column, line 6	1,2,6, 8-13
X	WO 97 02358 A (UNIV LELAND STANFORD JUNIOR ;UNIV BROWN RES FOUND (US)) 23 January 1997 (1997-01-23) example 10	1,2,6, 8-13
X	MARSDEN A F A ET AL.: "Engineering broader specificity into an antibiotic-producing polyketide synthase" SCIENCE, vol. 279, 9 January 1998 (1998-01-09), pages 199-202, XP002131320 figure 1	14
A	WO 98 01546 A (CORTES JESUS ;LEADLAY PETER F (GB); STAUNTON JAMES (GB); BIOTICA T) 15 January 1998 (1998-01-15) cited in the application page 6, line 15 -page 10, line 11 claims 1-6	1-13,15
A	BAO W ET AL.: "Reconstitution of the iterative type II polyketide synthase for tetracenomycin F2 biosynthesis" BIOCHEMISTRY, vol. 37, no. 22, June 1998 (1998-06), pages 8132-8138, XP002130659 page 8137, left-hand column, line 17 -right-hand column, line 20	1-4,6
A	KAKAVAS S J ET AL.: "Identification and characterization of the niddamycin polyketide synthase genes from Streptomyces caelestis" JOURNAL OF BACTERIOLOGY, vol. 179, no. 23, December 1997 (1997-12), pages 7515-7522, XP002130645 page 7518, right-hand column, line 33-49 page 7518, right-hand column, line 55 -page 7520, left-hand column, line 7 figures 4,6 page 7521, right-hand column, line 50 -page 7522, left-hand column, line 25	1-3,5-7
	-/-	



INTERNATIONAL SEARCH REPORT

Intern. Patent Application No.

PCT/GB 99/02044

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LEONARD KATZ: "Manipulation of modular polyketide synthases" CHEMICAL REVIEWS, vol. 97, no. 7, November 1997 (1997-11), pages 2557-2575, XP002103748 ISSN: 0009-2665 page 2565, right-hand column, paragraph C page 2571, right-hand column, paragraph C -page 2573; figure 10 ----	1-15
A	HOPWOOD D A: "Genetic contributions to understanding polyketid synthases" CHEMICAL REVIEWS, vol. 97, no. 7, November 1997 (1997-11), pages 2465-2497, XP002130647 page 2475, paragraph F1 -page 2477 page 2480, paragraph F5 table 2 ----	1-15
T	BISANG C ET AL.: "A chain initiation factor common to both modular and aromatic polyketide synthases" NATURE, vol. 401, 30 September 1999 (1999-09-30), pages 502-505, XP002130648 the whole document ----	1-15
T	WEISSMAN K J ET AL.: "Origin of starter units for erythromycin biosynthesis" BIOCHEMISTRY, vol. 37, no. 31, August 1998 (1998-08), pages 11012-11017, XP002130649 abstract page 11012 -page 11014, line 6 page 11016, right-hand column, line 3-29 -----	1,2,6, 8-13



INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 99/02044

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
See FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims No.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claim 14 relates to a compound defined by reference to a desirable characteristic, namely a difference related to the side chain provided by the starter unit. The claim covers all compounds having this characteristic, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. Moreover, the initial phase of the search revealed a large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim is impossible. In the present case, the claim so lacks support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for the part of claim 14 which appears to be supported and disclosed, namely the part relating to triketide lactones and 13-methyl-erythromycin as disclosed in examples 3, 5, and 8.



INTERNATIONAL SEARCH REPORT
information on patent family members

International Application No

PCT/GB 99/02044

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		AU 3451497 A	02-02-1998
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		CA 2259463 A	15-01-1998
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		EP 0910633 A	28-04-1999
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		PL 331285 A	05-07-1999
		AU 7666198 A	30-12-1998
		W0 9854308 A	03-12-1998

